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195. The therapeutic composition of claim 187 wherein fractions in the heparinic mucopolysaccharides have a molecular weight range of about 2,000 to about 8,000.

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196. The therapeutic composition of claim 187 include the heparinic mucopolysaccharide fractions which are soluble in an aqueous-alcoholic medium, insoluble in pure alcohol.

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197. The therapeutic method of claim 154 wherein the patient is exposed to risks of hypercoagulatability.

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198. The therapeutic method of claim 154 wherein the heparinic mucopolysaccharides have a USP titer of about 45 units per mg, a Yin-Wessler titer of about 160 units/mg and a ratio of Yin-Wessler to USP titer of about 3.55.

REMARKS

Favorable reconsideration of the claims is solicited.

The amendment to claims 154 and 161 bring out two aditional advantages of the method of use of the composition of the invention: that of decreasing the risk of hypercoagulation, (as disclosed on pages 5 and 7) and a slower and lower whole anticoagulation effect (as disclosed on pages 37, last paragraph and page 38, lines 3-5).

The claims have been rejected on the judicially

created doctrine of obviousness-type double-patenting as being unpatentable over the prior invention as set forth in claims 1-29 of U.S. Patent No. 4,486,420.

Applicants shall file, if the rejection is maintained, a disclaimer of the terminal portion of the term of the patent to issue from this application which extends beyond the term of the 4,486,420 patent.

A clean copy of the claims in this application has been presented to facilitate the examination by the Examiner.

With respect to the prior art previously made of record. The following additional comments are being submitted.

Anderson et al ("Anderson") fractionates a sample of commercial heparin by affinity chromatography and separates sub-fractions. Anderson collects heparin fractions in the range of 5,000 to 40,000 molecular weight. As is apparent from Fig. 1 (page 579) Anderson does not collect fractions of a molecular weight below 4,000 as is indicated by the authors' note with respect to the broken line of the curve on Fig. 1. In Fig. 2 there is shown the APTT and anti-X_a activities for the different fractions collected. Anderson's preparations I and II have APTT values higher than heparin (page 578).

Anderson does not show any interest in fractions of heparin below 5,000 of average molecular weight; the fractions are not even collected. Therefore, Anderson provides no teaching nor suggestion of the heparinic mucopolysaccharide compositions claimed, nor of course of their method of use.

Johnson et al ("Johnson") studies four heparin preparations of different mean molecular weights (HMW Na, LMW Na, a sodium and calcium preparation).

The high molecular weight heparin preparation of Johnson (22,000) is of a molecular weight range materially in excess of the upper limit of the molecular weight of the heparinic mucopolysaccharide fractions claimed herein. Even the low molecular weight heparin preparation of Johnson has an upper limit of molecular range also in excess of that called for by the claims and his heparin preparation does not have fractions below 4,000 molecular weight.

The sodium and calcium heparin preparations likewise exceed the upper limit set forth in the claims. There is no heparin preparation having a molecular weight range below 4,000. The whole anticoagulation values and the anti-Xa assays give values different from those of the invention.

Barrowcliffe et al ("Barrowcliffe") separates commercial heparin samples into five fractions of a molecular weight in the range of 6,000 to 30,000. The fractions of heparin studied by Barrowcliffe also do not conform to the molecular weight parameters set forth by the present claims and again quite importantly (like the other two references) are totally silent with respect to fractions of mucopolysaccharides having less than 7,000 molecular weight. Similar information is derivable from Figs. 1-4.

The three references are silent with respect to heparinic fractions having a cutoff point of molecular weight (as is set forth in the claims) and show a total lack of interest even for academic studies, in heparinic fractions having a molecular weight in the range from 2,000 to about 4,000 daltons which is called for by the claims. Indeed Anderson does not even bother collecting any fraction below 5,000 for assaying. Likewise Johnson, who collects three fractions labels a fraction which has a minimum of 4,000 "as low molecular weight fraction" and like Anderson does not collect any fraction of a molecular weight lower than 4,000. The same teaching is derived from Barrowcliffe. Thus the prior art taken together or individually is evidence of a lack of interest with respect to an essential component of the heparinic fractions claimed by applicants. Showing only a disinterest, the prior art throws no light whatsoever as to the properties (in terms of anti-coagulation and anti-thrombotic activities) on the products claimed herein. These have an ideal anti-thrombotic activity with significantly lowered risk of a patient hemorrhaging and of blood hypercoagulation. These are highly desirable and unexpected properties.

It is well established law that the prior art must provide a basis for modification to arrive at the invention as a whole with a reasonable expectation of success in achieving

the objects of the invention. In re Piasecki, 223 USPQ 785 (Fed. Cir. 1984); In Fromson v. Advanced Offset Plate, Inc., 225 USPQ 226, 31 (Fed. Cir. 1985), the Court stated:

> "The critical inquiry is whether there is something in the prior art as a whole to suggest the desirability and thus the obviousness of making the combination."

Here not only is there no suggestion in any one of the three references to lead or motivate one skilled in the art to the heparinic fractions claimed (or their method of use) but there is indeed a reinforcement of the lack of interest by one skilled in the art which each reference showed with respect to fractions below 5,000 or as claimed below 4,000.

It is interesting to note that the three publications are by substantial research groups in institutions of international reputation. Noteworthy too is that several of the authors are common on the three research teams, for instance, E.A. Johnson and T.W. Barrowcliffe. Notwithstanding that research cross-fertilization and the additional researchers (not common to the three teams), none of them had even the research curiosity to investigate in heparinic fractions below the 5,000 or 4,000 molecular weight range.

Further, the prior art is also totally silent as to the highly desirable properties - the delicate balance - of

anti-thrombotic to anti-coagulation activity as expressed by the Yen-Wessler to USP ratio as claimed. That ratio will be noted is particularly narrow: 3 to 5.

The lack of interest and thus of teaching of the prior art as to what is claimed is evidence of unobviousness. That the prior art teaches away from the claimed subject matter is one of the

> "highly probative, objective criteria fully capable of serving as the foundation for the legal conclusion of non-obviousness." W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303 (Fed. Cir. 1983), Cert. Denied, 105 S.Ct. 172 (1984).

For the reasons submitted, the subject matter claimed is useful and unobvious. Applicants have made a highly meritorious contribution to the medical arts and deserve patent protection. Such is respectfully requested.

It is respectfully asked that the Examiner call the undersigned before acting on the case so that in the event that the claims are not all allowable, an interview can be scheduled.

Respectfully submitted,

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